NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Sacubitril/Valsartan

Trial Indication(s)

Heart failure with preserved ejection fraction

Protocol Number

CLCZ696D2302

Protocol Title

A 24-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate the effect of LCZ696 on NT-proBNP, exercise capacity, symptoms and safety compared to individualized medical management of comorbidities in patients with heart failure and preserved ejection fraction

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase 3

Study Start/End Dates

Study Start Date: August 2017 (Actual)
Primary Completion Date: October 2019 (Actual)
Study Completion Date: October 2019 (Actual)

Study Design/Methodology

This study was a 24-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate sacubitril/valsartan compared to individualized medical therapy on NT proBNP, exercise capacity, symptoms and QoL in patients with heart failure and preserved left ventricular ejection (HFpEF) fraction (LVEF > 40%). Patients were initially stratified into one of three strata according to prior treatment for comorbidities: Angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB) or no prior renin angiotensin system inhibitors (RASi). Patients in each stratum were randomized in a 1:1 ratio and received either sacubitril/valsartan or comparator (i.e. enalapril for patients in ACEi strata, valsartan for patients in the ARB strata and placebo for patients in the No RASi strata). There was no designated proportion of patients planned in each stratum; the strata were populated based upon the patient's prior treatment regimen. The study consisted of a screening epoch of up to 2 weeks and a randomized treatment epoch of 24 weeks, which included a 1 to 4 week study drug up-titration epoch followed by a 20 to 23 week maintenance epoch.

Centers

396 centers in 32 countries: Germany(71), United States(32), Hungary(6), Slovakia (Slovak Republic)(20), Estonia(4), Spain(17), United Kingdom(9), France(10), Latvia(4), Czech Republic(18), Portugal(8), Canada(5), Lithuania(3), Argentina(18), India(11), Belgium(5), Denmark(3), Bulgaria(15), Italy(12), Austria(5), Thailand(6), Netherlands(11), Turkey(14), Russia(21), Colombia(6), Brazil(13), Peru(7), Israel(6), Guatemala(11), Romania(16), Serbia(5), Mexico(4)

Objectives:

Primary objectives:
To demonstrate that sacubitril/valsartan is superior to individualized medical therapy for comorbidities in reducing N-terminal pro-brain natriuretic peptide (NT-proBNP) from baseline after 12 weeks of treatment

To demonstrate that sacubitril/valsartan is superior to individualized medical therapy for comorbidities in improving exercise capacity as assessed by the six-minute walk test (6MWT) at Week 24 in a subset of patients

Secondary objectives:
To compare sacubitril/valsartan to individualized medical therapy for comorbidities on mean change of Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS) at Week 24

To compare sacubitril/valsartan to individualized medical therapy for comorbidities on proportion of patients with ≥ 5-points change in KCCQ CSS at Week 24 (separate analyses for ≥ 5-points improvement and ≥ 5-points deterioration)

To compare sacubitril/valsartan to individualized medical therapy for comorbidities in improving New York Heart Association (NYHA) functional class at Week 24

To compare sacubitril/valsartan to individualized medical therapy for comorbidities in improving symptoms as assessed by The Short Form (36) Health Survey (SF-36) physical component summary (PCS) score at Week 24

Test Product (s), Dose(s), and Mode(s) of Administration

The following study medications were provided:

- LCZ696 (sacubitril/valsartan) 50 mg (24 mg/26 mg), 100 mg (49 mg/51 mg) and 200 mg (97 mg/103 mg) tablets
- Placebo to match LCZ696 50 mg, 100 mg and 200 mg tablets
- Enalapril 2.5 mg, 5 mg and 10 mg tablets
- Placebo to match enalapril 2.5 mg, 5 mg and 10 mg tablets
- Valsartan 40 mg, 80 mg and 160 mg tablets
- Placebo to match valsartan 40 mg, 80 mg and 160 mg tablets

Statistical Methods

The following primary null hypotheses were included in the testing strategy.
H1: LCZ696 is no better than individualized medical therapy (IMT) in change from baseline in log(NT-proBNP) at Week 12 in the overall study population

H2: LCZ696 is no better than IMT in change from baseline in 6MWD at Week 24 in patients with baseline 6MWD (B6MWD) ranging from 100 m to 450 m.

The following secondary null hypotheses were included in the testing strategy.
H3: LCZ696 is no better than IMT in change from baseline in KCCQ CSS at Week 24 in the overall study population.

H4: LCZ696 is no better than IMT in NYHA change from baseline at Week 24 in the overall study population.

Each null hypothesis was tested against the one-sided alternative that LCZ696 is better than IMT in the corresponding variable. In order to control the family-wise type-I error rate at the one-sided 0.025 significance level, a sequentially rejective multiple testing procedure was employed, whereby H1 and H2 were tested first at initially assigned level of one-sided (9/10) × α = 0.0225 and one-sided (1/10) × α = 0.0025, accordingly.

The HI, H2, and H3 were tested based on the corresponding mixed models for repeated measures. For H4 was tested based on a proportional cumulative odds model. In addition, the improvement and the deterioration in 6MWD, KCCQ CSS, NYHA, SF-36 PCS were analyzed separately using longitudinal binary logistic regression models.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

•Left ventricular ejection fraction (LVEF) >40% by echo within 6 months prior to study entry or during the screening epoch
•Symptom(s) of heart failure (HF) requiring treatment with diuretics (including loop, or thiazide diuretics, or mineralocorticoid antagonist [MRAs]) for at least 30 days prior to study entry
•NYHA class II-IV
•Structural heart disease (left atrial enlargement or left ventricular hypertrophy) documented by echocardiogram.
•NT-proBNP > 220 pg/mL for patients with no atrial fibrillation/atrial flutter (AF) or >600 pg/mL for patients with AF
•KCCQ clinical summary score < 75
• Patients on ACEi or ARB therapy must have a history of HTN

Exclusion Criteria:

•Any prior measurement of LVEF ≤ 40%, under stable conditions
•Acute coronary syndrome (including MI), cardiac surgery, other major CV surgery within 3 months , or urgent percutaneous coronary intervention (PCI) within 3 months or an elective PCI within 30 days prior to study entry
•Any clinical event within the 6 months prior to Visit 1 that could have reduced the LVEF (eg MI, coronary artery bypass graft [CABG]), unless an echo measurement was performed after the event confirming the LVEF to be >40%
•Current (within 30 days from Visit 1) acute decompensated HF requiring therapy.
•Current (within 30 days from Visit 1) use of renin inhibitor(s), dual RAS blockade or
LCZ696
•History of hypersensitivity to LCZ696 or its components
• Patients with a known history of angioedema
•Walk distance primarily limited by non-cardiac comorbid conditions at study entry
•Alternative reason for shortness of breath such as: significant pulmonary disease or severe COPD, hemoglobin (Hgb) <10 g/dL males and < 9.5 g/dL females, or body mass index (BMI) > 40 kg/m^2.
•Systolic blood pressure (SBP) ≥ 180 mmHg at study entry, or SBP >150 mmHg and <180 mmHg at study entry unless the patient is receiving 3 or more antihypertensive drugs, or SBP < 110 mmHg at study entry.
•Patients with HbA1c > 7.5% not treated for diabetes
•Patients with prior major organ transplant or intent to transplant (ie on transplant list)
•eGFR < 30 ml/min/1.73 m^2 as measured by MDRD at screening
•Serum potassium > 5.2 mmol /L (or equivalent plasma potassium value) at study entry
•History or presence of any other disease with a life expectancy of < 3 years
•Pregnant or nursing women or women of child-bearing potential unless they are using highly effective methods of contraception

Participant Flow Table

Overall Study

	Sacubitril/Valsartan (LCZ696)	Individualized Medical Therapy (IMT) Comparator	Total
Arm/Group Description	All patients who fulfilled the inclusion/exclusion criteria were stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata received LCZ696 or valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and one tablet from the comparator pack. Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo).	Patients randomized to the comparator arm received either enalapril (ACE stratum) valsartan (ARB stratum) or LCZ696 matching placebo (no RASi stratum). Patients in the ACE stratum randomized to comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB stratum randomized to comparator received valsartan in titrated doses from level 1 up	

	In the LCZ696 arm, patients received active LCZ696 in titrated doses from level 1 up to level 3 (50 mg, 100 mg and 200 mg twice daily orally).	to level 3 (40 mg , 80 mg and 160 mg twice daily). Patients in the no RASi stratum randomized to comparator received LCZ696 matching placebo.	
Started	1286	1286	2572
Completed	1235	1236	2471
Not Completed	51	50	101
Physician Decision	0	4	4
Death	23	17	40
Withdrawal by Subject	19	25	44
Lost to Follow-up	2	0	2
Adverse Event	2	3	5
Technical problems	5	1	6

Baseline Characteristics

	Sacubitril/Valsartan (LCZ696)	Individualized Medical Therapy (IMT) Comparator	Total
Arm/Group Description	All patients who fulfilled the inclusion/exclusion criteria were stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata received LCZ696 or valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and one tablet from the comparator pack.	Patients randomized to the comparator arm received either enalapril (ACE stratum) valsartan (ARB stratum) or LCZ696 matching placebo (no RASi stratum). Patients in the ACE stratum randomized to comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB stratum randomized to	

	Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo). In the LCZ696 arm, patients received active LCZ696 in titrated doses from level 1 up to level 3 (50 mg, 100 mg and 200 mg twice daily orally).	comparator received valsartan in titrated doses from level 1 up to level 3 (40 mg , 80 mg and 160 mg twice daily). Patients in the no RASi stratum randomized to comparator received LCZ696 matching placebo.	
Number of Participants [units: participants]	1281	1285	2566
Sex: Female, Male (units:) Count of Participants (Not Applicable)			
Female	643	658	1301
Male	638	627	1265
Age, Customized (units: Participants) Count of Participants (Not Applicable)			
<65 years	196	221	417
>=65 years	1085	1064	2149
Race/Ethnicity, Customized (units: Participants)			

Caucasian	1112	1117	2229
Black	11	16	27
Asian	56	59	115
Native American	39	33	72
Pacific Islander	0	1	1
Unknown	4	3	7
Other	59	56	115

Primary Outcome Result(s)

Change from baseline in N-terminal pro-brain natriuretic peptide (NT-proBNP) at Week 12
(Time Frame: Baseline, week 12)

	Sacubitril/Valsartan (LCZ696)	Individualized Medical Therapy (IMT) Comparator
Arm/Group Description	All patients who fulfilled the inclusion/exclusion criteria were stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata received LCZ696 or	Patients randomized to the comparator arm received either enalapril (ACE stratum) valsartan (ARB stratum) or LCZ696 matching placebo (no RASi stratum). Patients in the ACE stratum randomized to

	valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and one tablet from the comparator pack. Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo). In the LCZ696 arm, patients received active LCZ696 in titrated doses from level 1 up to level 3 (50 mg, 100 mg and 200 mg twice daily orally).	comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB stratum randomized to comparator received valsartan in titrated doses from level 1 up to level 3 (40 mg , 80 mg and 160 mg twice daily). Patients in the no RASi stratum randomized to comparator received LCZ696 matching placebo.
Number of Participants Analyzed [units: participants]	1281	1285
Change from baseline in N-terminal pro-brain natriuretic peptide		

(NT-proBNP) at Week 12 (units: Percentage) Geometric Mean (95% Confidence Interval)		
Week 12 (n=1203, n=1216)	0.8218 (0.7955 to 0.8489)	0.9828 (0.9515 to 1.0151)

Statistical Analysis

Groups	Sacubitril/Valsartan (LCZ696), Individualized Medical Therapy (IMT) Comparator	Week 12
P Value	<.0001	
Method	Mixed Models Analysis	
Other Geometric Mean Ratio	0.8362	
95 % Confidence Interval 2-Sided	0.7987 to 0.8754	

Change from baseline in 6 minute walk distance (6MWD) at Week 24
(Time Frame: Baseline, week 24)

	Sacubitril/Valsartan (LCZ696)	**Individualized Medical Therapy (IMT) Comparator**
Arm/Group Description	All patients who fulfilled the inclusion/exclusion	Patients randomized to the

criteria were stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata received LCZ696 or valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and one tablet from the comparator pack. Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo). In the LCZ696 arm, patients received active LCZ696 in titrated doses from level 1 up to level 3 (50 mg, 100 mg and 200 mg twice daily	comparator arm received either enalapril (ACE stratum) valsartan (ARB stratum) or LCZ696 matching placebo (no RASi stratum). Patients in the ACE stratum randomized to comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB stratum randomized to comparator received valsartan in titrated doses from level 1 up to level 3 (40 mg , 80 mg and 160 mg twice daily). Patients in the no RASi stratum randomized to

	orally).	comparator received LCZ696 matching placebo.
Number of Participants Analyzed [units: participants]	1154	1159
Change from baseline in 6 minute walk distance (6MWD) at Week 24 (units: Meter) Mean (95% Confidence Interval)		
(n=1082, n=1075)	9.6935 (5.4310 to 13.9559)	12.1920 (7.9202 to 16.4638)

Statistical Analysis

Groups	Sacubitril/Valsartan (LCZ696), Individualized Medical Therapy (IMT) Comparator
P Value	0.4164
Method	Mixed Models Analysis
Mean Difference (Net)	-2.4985
95 % Confidence Interval	-8.5267 to 3.52297

Secondary Outcome Result(s)

Mean change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS) at Week 24
(Time Frame: Baseline, Week 24)

	Sacubitril/Valsartan (LCZ696)	Individualized Medical Therapy (IMT) Comparator
Arm/Group Description	All patients who fulfilled the inclusion/exclusion criteria were stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata received LCZ696 or valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and	Patients randomized to the comparator arm received either enalapril (ACE stratum) valsartan (ARB stratum) or LCZ696 matching placebo (no RASi stratum). Patients in the ACE stratum randomized to comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB

	one tablet from the comparator pack. Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo). In the LCZ696 arm, patients received active LCZ696 in titrated doses from level 1 up to level 3 (50 mg, 100 mg and 200 mg twice daily orally).	stratum randomized to comparator received valsartan in titrated doses from level 1 up to level 3 (40 mg , 80 mg and 160 mg twice daily). Patients in the no RASi stratum randomized to comparator received LCZ696 matching placebo.
Number of Participants Analyzed [units: participants]	1281	1285
Mean change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS) at Week 24 (units: Scores on a scale) Mean (95% Confidence Interval)		
(n=1207, n=1210)	12.3399 (11.3151 to 13.3647)	11.8168 (10.7922 to

12.8415)

Statistical Analysis

Groups	Sacubitril/Valsartan (LCZ696), Individualized Medical Therapy (IMT) Comparator
P Value	0.4791
Method	Mixed Models Analysis
Mean Difference (Net)	0.5231
95 % Confidence Interval 2-Sided	-0.9258 to 1.9720

Percentage of patients with ≥ 5-points deterioration in KCCQ CSS at Week 24
(Time Frame: Baseline, Week 24)

	Sacubitril/Valsartan (LCZ696)	**Individualized Medical Therapy (IMT) Comparator**
Arm/Group Description	All patients who fulfilled the inclusion/exclusion criteria were stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no	Patients randomized to the comparator arm received either enalapril (ACE stratum) valsartan (ARB stratum) or LCZ696

	RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata received LCZ696 or valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and one tablet from the comparator pack. Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo). In the LCZ696 arm, patients received active LCZ696 in titrated doses from level 1 up to level 3 (50 mg, 100 mg and 200 mg twice daily orally).	matching placebo (no RASi stratum). Patients in the ACE stratum randomized to comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB stratum randomized to comparator received valsartan in titrated doses from level 1 up to level 3 (40 mg , 80 mg and 160 mg twice daily). Patients in the no RASi stratum randomized to comparator received LCZ696 matching placebo.
Number of	1281	1285

Participants Analyzed [units: participants]		
Percentage of patients with ≥ 5-points deterioration in KCCQ CSS at Week 24 (units: Percentage of participants)		
(n=1207, n=1210)	15.49	16.69

Statistical Analysis

Groups	Sacubitril/Valsartan (LCZ696), Individualized Medical Therapy (IMT) Comparator
P Value	0.5294
Method	Other longitudinal binary logistic regression
Odds Ratio (OR)	0.8993
95 % Confidence Interval 2-Sided	0.6461 to 1.2518

Percentage of patients with ≥ 5-points improvement in KCCQ CSS at Week 24
(Time Frame: Baseline, Week 24)

	Sacubitril/Valsartan (LCZ696)	**Individualized Medical Therapy (IMT) Comparator**

Arm/Group Description	All patients who fulfilled the inclusion/exclusion criteria were stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata received LCZ696 or valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and one tablet from the comparator pack. Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo). In the LCZ696 arm, patients received active LCZ696 in titrated doses from	Patients randomized to the comparator arm received either enalapril (ACE stratum) valsartan (ARB stratum) or LCZ696 matching placebo (no RASi stratum). Patients in the ACE stratum randomized to comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB stratum randomized to comparator received valsartan in titrated doses from level 1 up to level 3 (40 mg , 80 mg and 160 mg twice daily).

	level 1 up to level 3 (50 mg, 100 mg and 200 mg twice daily orally).	Patients in the no RASi stratum randomized to comparator received LCZ696 matching placebo.
Number of Participants Analyzed [units: participants]	1281	1285
Percentage of patients with ≥ 5-points improvement in KCCQ CSS at Week 24 (units: Percentage of participants)		
(n=1207, n=1210)	67.94	65.70

Statistical Analysis

Groups	Sacubitril/Valsartan (LCZ696), Individualized Medical Therapy (IMT) Comparator
P Value	0.4938
Method	Other longitudinal binary logistic regression
Odds Ratio (OR)	1.1060

95
% Confidence Interval 0.8287 to 1.4760
2-Sided

Change from baseline in NYHA functional class at Week 24
(Time Frame: Baseline, week 24)

	Sacubitril/Valsartan (LCZ696)	Individualized Medical Therapy (IMT) Comparator
Arm/Group Description	All patients who fulfilled the inclusion/exclusion criteria were stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata received LCZ696 or valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and one tablet from the	Patients randomized to the comparator arm received either enalapril (ACE stratum) valsartan (ARB stratum) or LCZ696 matching placebo (no RASi stratum). Patients in the ACE stratum randomized to comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB stratum

	comparator pack. Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo). In the LCZ696 arm, patients received active LCZ696 in titrated doses from level 1 up to level 3 (50 mg, 100 mg and 200 mg twice daily orally).	randomized to comparator received valsartan in titrated doses from level 1 up to level 3 (40 mg , 80 mg and 160 mg twice daily). Patients in the no RASi stratum randomized to comparator received LCZ696 matching placebo.
Number of Participants Analyzed [units: participants]	1281	1285
Change from baseline in NYHA functional class at Week 24 (units: Percentage of Participants)		
Improved	23.62	24.00
Unchanged	72.23	71.68
Worsened	4.15	4.31

Statistical Analysis

Groups Sacubitril/Valsartan

	(LCZ696), Individualized Medical Therapy (IMT) Comparator
P Value	0.8314
Method	Other Proportional cumulative odds model
Odds Ratio (OR)	0.9798
95 % Confidence Interval 2-Sided	0.8122 to 1.1820

Change from baseline in The Short Form 36 Health Survey (SF-36) physical component summary (PCS) score at week 24
(Time Frame: Baseline, Week 24)

	Sacubitril/Valsartan (LCZ696)	**Individualized Medical Therapy (IMT) Comparator**
Arm/Group Description	All patients who fulfilled the inclusion/exclusion criteria were stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata	Patients randomized to the comparator arm received either enalapril (ACE stratum) valsartan (ARB stratum) or LCZ696 matching placebo (no RASi stratum). Patients in the ACE stratum

	received LCZ696 or valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and one tablet from the comparator pack. Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo). In the LCZ696 arm, patients received active LCZ696 in titrated doses from level 1 up to level 3 (50 mg, 100 mg and 200 mg twice daily orally).	randomized to comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB stratum randomized to comparator received valsartan in titrated doses from level 1 up to level 3 (40 mg , 80 mg and 160 mg twice daily). Patients in the no RASi stratum randomized to comparator received LCZ696 matching placebo.
Number of Participants Analyzed [units: participants]	1281	1285
Change from baseline in The Short Form 36		

Health Survey (SF-36) physical component summary (PCS) score at week 24 (units: Scores on a scale) Mean (95% Confidence Interval)		
(n=1185, n=1191)	2.5405 (2.0787 to 3.0023)	2.6975 (2.2360 to 3.1590)

Statistical Analysis

Groups	Sacubitril/Valsartan (LCZ696), Individualized Medical Therapy (IMT) Comparator
P Value	0.6370
Method	Mixed Models Analysis
Mean Difference (Net)	-0.1570
95 % Confidence Interval	-0.8093 to 0.4953

Safety Results

All-Cause Mortality

	Sacubitril/Valsartan (LCZ696)	**Individualized Medical**	**Total N = 2564**

	N = 1280	Therapy (IMT) N = 1284	
Arm/Group Description	All patients who fulfilled the inclusion/exclusion criteria were stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata received LCZ696 or valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and one tablet from the comparator pack. Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo). In the LCZ696 arm, patients received	Patients randomized to the comparator arm received either enalapril (ACE stratum) valsartan (ARB stratum) or LCZ696 matching placebo (no RASi stratum). Patients in the ACE stratum randomized to comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB stratum randomized to comparator received valsartan in titrated doses from level 1 up to level 3 (40 mg , 80 mg	Total

	active LCZ696 in titrated doses from level 1 up to level 3 (50 mg, 100 mg and 200 mg twice daily orally).	and 160 mg twice daily). Patients in the no RASi stratum randomized to comparator received LCZ696 matching placebo.	
Total participants affected	23 (1.80%)	17 (1.32%)	40 (1.56%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of approx. 2 years.
Additional Description	Any sign or symptom that occurs during the study treatment plus the 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (22.1)
Assessment Type for Table Default	Systematic Assessment

	Sacubitril/Valsartan (LCZ696) N = 1280	**Individualized Medical Therapy (IMT) N = 1284**	**Total N = 2564**
Arm/Group	All patients who	Patients	Total

Description	fulfilled the inclusion/exclusion criteria were stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata received LCZ696 or valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and one tablet from the comparator pack. Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo). In the LCZ696 arm, patients received active LCZ696 in titrated doses from level 1 up to level 3 (50 mg, 100 mg and	randomized to the comparator arm received either enalapril (ACE stratum) valsartan (ARB stratum) or LCZ696 matching placebo (no RASi stratum). Patients in the ACE stratum randomized to comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB stratum randomized to comparator received valsartan in titrated doses from level 1 up to level 3 (40 mg , 80 mg and 160 mg twice daily). Patients in the no RASi

	200 mg twice daily orally).	stratum randomized to comparator received LCZ696 matching placebo.	
Total participants affected	186 (14.53%)	191 (14.88%)	377 (14.70%)
Blood and lymphatic system disorders			
Anaemia*	2 (0.16%)	3 (0.23%)	5 (0.20%)
Febrile neutropenia*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Lymphadenopathy*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Cardiac disorders			
Acute coronary syndrome*	4 (0.31%)	1 (0.08%)	5 (0.20%)
Acute myocardial infarction*	2 (0.16%)	4 (0.31%)	6 (0.23%)
Angina pectoris*	8 (0.63%)	8 (0.62%)	16 (0.62%)
Angina unstable*	6 (0.47%)	7 (0.55%)	13 (0.51%)
Aortic valve disease*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Aortic valve incompetence*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Atrial fibrillation*	13 (1.02%)	17 (1.32%)	30 (1.17%)
Atrial flutter*	4 (0.31%)	2 (0.16%)	6 (0.23%)
Atrial tachycardia*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Atrioventricular block	2 (0.16%)	3 (0.23%)	5 (0.20%)

complete*			
Atrioventricular block second degree*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Bradycardia*	1 (0.08%)	2 (0.16%)	3 (0.12%)
Cardiac arrest*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Cardiac failure*	21 (1.64%)	31 (2.41%)	52 (2.03%)
Cardiac failure acute*	3 (0.23%)	9 (0.70%)	12 (0.47%)
Cardiac failure chronic*	2 (0.16%)	1 (0.08%)	3 (0.12%)
Cardiac failure congestive*	2 (0.16%)	7 (0.55%)	9 (0.35%)
Cardiac perforation*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Cardiogenic shock*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Cor pulmonale acute*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Coronary artery disease*	4 (0.31%)	1 (0.08%)	5 (0.20%)
Dressler's syndrome*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Left ventricular failure*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Mitral valve incompetence*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Myocardial infarction*	1 (0.08%)	4 (0.31%)	5 (0.20%)
Myocardial ischaemia*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Pericardial effusion*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Sinus arrest*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Sinus node dysfunction*	0 (0.00%)	1 (0.08%)	1 (0.04%)

Supraventricular tachycardia*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Congenital, familial and genetic disorders			
Mitochondrial myopathy*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Ear and labyrinth disorders			
Vertigo*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Vertigo positional*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Vestibular ataxia*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Eye disorders			
Cataract*	1 (0.08%)	2 (0.16%)	3 (0.12%)
Eye haemorrhage*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Iris neovascularisation*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Macular hole*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Retinal artery occlusion*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Visual acuity reduced*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Gastrointestinal disorders			
Abdominal hernia*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Abdominal pain*	0 (0.00%)	2 (0.16%)	2 (0.08%)
Diarrhoea*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Duodenal ulcer	1 (0.08%)	0 (0.00%)	1 (0.04%)

perforation*			
Gastric haemorrhage*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Gastritis*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Gastritis erosive*	0 (0.00%)	2 (0.16%)	2 (0.08%)
Gastrointestinal haemorrhage*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Gastrointestinal ulcer haemorrhage*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Haemorrhagic erosive gastritis*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Ileus*	2 (0.16%)	1 (0.08%)	3 (0.12%)
Incarcerated inguinal hernia*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Inguinal hernia*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Intestinal perforation*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Large intestine polyp*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Mallory-Weiss syndrome*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Rectal polyp*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Upper gastrointestinal haemorrhage*	0 (0.00%)	2 (0.16%)	2 (0.08%)
General disorders and administration site conditions			
Cardiac death*	2 (0.16%)	0 (0.00%)	2 (0.08%)
Chest pain*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Death*	0 (0.00%)	2 (0.16%)	2 (0.08%)

Fatigue*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Gait disturbance*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Generalised oedema*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Malaise*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Multiple organ dysfunction syndrome*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Non-cardiac chest pain*	0 (0.00%)	2 (0.16%)	2 (0.08%)
Oedema peripheral*	1 (0.08%)	2 (0.16%)	3 (0.12%)
Pyrexia*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Sudden death*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Hepatobiliary disorders			
Bile duct stenosis*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Bile duct stone*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Cholangitis*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Cholecystitis*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Cholelithiasis*	2 (0.16%)	1 (0.08%)	3 (0.12%)
Hepatic congestion*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Liver disorder*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Infections and infestations			
Appendicitis*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Bronchitis*	3 (0.23%)	2 (0.16%)	5 (0.20%)
Campylobacter	0 (0.00%)	1 (0.08%)	1 (0.04%)

gastroenteritis*			
Cellulitis*	3 (0.23%)	0 (0.00%)	3 (0.12%)
Cholangitis infective*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Cutaneous leishmaniasis*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Cystitis*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Dengue fever*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Device related infection*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Diverticulitis*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Endocarditis*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Erysipelas*	2 (0.16%)	3 (0.23%)	5 (0.20%)
Gastroenteritis*	2 (0.16%)	1 (0.08%)	3 (0.12%)
Hepatitis C*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Infection*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Infectious pleural effusion*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Influenza*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Localised infection*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Lower respiratory tract infection*	3 (0.23%)	0 (0.00%)	3 (0.12%)
Nasopharyngitis*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Pneumococcal sepsis*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Pneumonia*	13 (1.02%)	13 (1.01%)	26 (1.01%)
Pneumonia bacterial*	1 (0.08%)	0 (0.00%)	1 (0.04%)

Post procedural sepsis*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Postoperative wound infection*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Pulmonary sepsis*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Pyelonephritis*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Respiratory tract infection*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Sepsis*	2 (0.16%)	1 (0.08%)	3 (0.12%)
Upper respiratory tract infection*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Urinary tract infection*	4 (0.31%)	1 (0.08%)	5 (0.20%)
Wound infection*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Injury, poisoning and procedural complications			
Agitation postoperative*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Animal bite*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Contusion*	2 (0.16%)	0 (0.00%)	2 (0.08%)
Facial bones fracture*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Fall*	0 (0.00%)	4 (0.31%)	4 (0.16%)
Femoral neck fracture*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Fractured ischium*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Fractured sacrum*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Head injury*	0 (0.00%)	1 (0.08%)	1 (0.04%)

Hip fracture*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Limb injury*	0 (0.00%)	2 (0.16%)	2 (0.08%)
Meniscus injury*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Multiple injuries*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Post procedural complication*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Post procedural haemorrhage*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Pubis fracture*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Seroma*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Spinal fracture*	1 (0.08%)	2 (0.16%)	3 (0.12%)
Subdural haematoma*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Thoracic vertebral fracture*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Upper limb fracture*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Investigations			
Blood urine present*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Haemoglobin decreased*	1 (0.08%)	0 (0.00%)	1 (0.04%)
International normalised ratio increased*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Liver function test abnormal*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Metabolism and nutrition disorders			

Diabetes mellitus*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Diabetic metabolic decompensation*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Hyperkalaemia*	1 (0.08%)	2 (0.16%)	3 (0.12%)
Hypoglycaemia*	3 (0.23%)	0 (0.00%)	3 (0.12%)
Hypokalaemia*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Hyponatraemia*	2 (0.16%)	1 (0.08%)	3 (0.12%)
Malnutrition*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Musculoskeletal and connective tissue disorders			
Arthralgia*	0 (0.00%)	2 (0.16%)	2 (0.08%)
Back pain*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Bone pain*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Intervertebral disc protrusion*	3 (0.23%)	0 (0.00%)	3 (0.12%)
Musculoskeletal chest pain*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Myalgia*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Osteoarthritis*	1 (0.08%)	2 (0.16%)	3 (0.12%)
Osteochondrosis*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Osteoporosis*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Pathological fracture*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Rheumatoid arthritis*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Spinal pain*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Spinal stenosis*	0 (0.00%)	4 (0.31%)	4 (0.16%)

Spondylolisthesis*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma*	1 (0.08%)	2 (0.16%)	3 (0.12%)
Bladder neoplasm*	2 (0.16%)	0 (0.00%)	2 (0.08%)
Breast cancer*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Cervix carcinoma*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Colon adenoma*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Colon cancer*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Gastric cancer*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Gastrointestinal carcinoma*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Laryngeal cancer*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Lung cancer metastatic*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Lung neoplasm malignant*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Lymphoma*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Malignant melanoma*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Metastases to liver*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Metastases to spine*	2 (0.16%)	0 (0.00%)	2 (0.08%)
Metastatic neoplasm*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Nasal cavity cancer*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Neuroendocrine	1 (0.08%)	0 (0.00%)	1 (0.04%)

tumour*			
Oesophageal squamous cell carcinoma*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Plasma cell myeloma*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Prostate cancer*	2 (0.16%)	0 (0.00%)	2 (0.08%)
Prostate cancer metastatic*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Rectal adenocarcinoma*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Renal cell carcinoma*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Renal neoplasm*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Spinal meningioma benign*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Squamous cell carcinoma*	0 (0.00%)	2 (0.16%)	2 (0.08%)
Urinary tract neoplasm*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Nervous system disorders			
Carotid artery aneurysm*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Cerebral haemorrhage*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Cerebral infarction*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Cerebrovascular accident*	2 (0.16%)	0 (0.00%)	2 (0.08%)
Dementia*	0 (0.00%)	1 (0.08%)	1 (0.04%)

Diabetic neuropathy*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Dizziness*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Encephalopathy*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Haemorrhagic transformation stroke*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Hepatic encephalopathy*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Hypoxic-ischaemic encephalopathy*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Ischaemic stroke*	0 (0.00%)	6 (0.47%)	6 (0.23%)
Parkinson's disease*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Sciatica*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Sensory disturbance*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Syncope*	2 (0.16%)	2 (0.16%)	4 (0.16%)
Transient ischaemic attack*	4 (0.31%)	0 (0.00%)	4 (0.16%)
Product issues			
Device breakage*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Psychiatric disorders			
Alcohol abuse*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Depression*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Suicide attempt*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Renal and urinary disorders			
Acute kidney injury*	4 (0.31%)	7 (0.55%)	11 (0.43%)

Diabetic nephropathy*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Haematuria*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Nephritic syndrome*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Nephrolithiasis*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Renal failure*	3 (0.23%)	0 (0.00%)	3 (0.12%)
Renal impairment*	2 (0.16%)	0 (0.00%)	2 (0.08%)
Renal injury*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Urinary retention*	0 (0.00%)	2 (0.16%)	2 (0.08%)
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Acute respiratory failure*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Asthma*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Chronic obstructive pulmonary disease*	3 (0.23%)	4 (0.31%)	7 (0.27%)
Chronic respiratory failure*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Cough*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Dyspnoea*	1 (0.08%)	6 (0.47%)	7 (0.27%)
Epistaxis*	0 (0.00%)	3 (0.23%)	3 (0.12%)
Pneumonitis*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Pulmonary embolism*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Pulmonary	1 (0.08%)	0 (0.00%)	1 (0.04%)

hypertension*			
Pulmonary oedema*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Respiratory failure*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Skin and subcutaneous tissue disorders			
Angioedema*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Diabetic foot*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Skin ulcer*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Vascular disorders			
Accelerated hypertension*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Aortic dissection*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Aortic stenosis*	1 (0.08%)	1 (0.08%)	2 (0.08%)
Arterial rupture*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Deep vein thrombosis*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Haematoma*	1 (0.08%)	2 (0.16%)	3 (0.12%)
Hypertension*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Hypertensive crisis*	2 (0.16%)	1 (0.08%)	3 (0.12%)
Hypertensive urgency*	0 (0.00%)	2 (0.16%)	2 (0.08%)
Hypotension*	6 (0.47%)	2 (0.16%)	8 (0.31%)
Iliac artery stenosis*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Orthostatic hypotension*	0 (0.00%)	1 (0.08%)	1 (0.04%)

Peripheral artery occlusion*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Peripheral vascular disorder*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Shock*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Thrombophlebitis*	0 (0.00%)	1 (0.08%)	1 (0.04%)
Thrombosis*	1 (0.08%)	0 (0.00%)	1 (0.04%)
Vasculitis*	1 (0.08%)	0 (0.00%)	1 (0.04%)

* Non-systematic Assessment

Other Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of approx. 2 years.
Additional Description	Any sign or symptom that occurs during the study treatment plus the 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (22.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	2%

	Sacubitril/Valsartan (LCZ696) N = 1280	**Individualized Medical Therapy (IMT) N = 1284**	**Total N = 2564**
Arm/Group Description	All patients who fulfilled the inclusion/exclusion criteria were stratified before randomization based	Patients randomized to the comparator arm received either enalapril	Total

	upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata received LCZ696 or valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and one tablet from the comparator pack. Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo). In the LCZ696 arm, patients received active LCZ696 in titrated doses from level 1 up to level 3 (50 mg, 100 mg and 200 mg twice daily orally).	(ACE stratum) valsartan (ARB stratum) or LCZ696 matching placebo (no RASi stratum). Patients in the ACE stratum randomized to comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB stratum randomized to comparator received valsartan in titrated doses from level 1 up to level 3 (40 mg , 80 mg and 160 mg twice daily). Patients in the no RASi stratum randomized to comparator received LCZ696

		matching placebo.	
Total participants affected	964 (75.31%)	832 (64.80%)	1796 (70.05%)
Blood and lymphatic system disorders			
Anaemia*	17 (1.33%)	28 (2.18%)	45 (1.76%)
Cardiac disorders			
Atrial fibrillation*	44 (3.44%)	43 (3.35%)	87 (3.39%)
Cardiac failure*	34 (2.66%)	43 (3.35%)	77 (3.00%)
Gastrointestinal disorders			
Diarrhoea*	43 (3.36%)	42 (3.27%)	85 (3.32%)
General disorders and administration site conditions			
Fatigue*	38 (2.97%)	21 (1.64%)	59 (2.30%)
Oedema peripheral*	43 (3.36%)	35 (2.73%)	78 (3.04%)
Infections and infestations			
Bronchitis*	29 (2.27%)	35 (2.73%)	64 (2.50%)
Influenza*	33 (2.58%)	23 (1.79%)	56 (2.18%)
Nasopharyngitis*	35 (2.73%)	60 (4.67%)	95 (3.71%)
Urinary tract infection*	49 (3.83%)	35 (2.73%)	84 (3.28%)
Investigations			
Blood creatinine	27 (2.11%)	22 (1.71%)	49 (1.91%)

increased*			
Blood potassium increased*	26 (2.03%)	10 (0.78%)	36 (1.40%)
Glomerular filtration rate decreased*	137 (10.70%)	150 (11.68%)	287 (11.19%)
Urine albumin/creatinine ratio increased*	157 (12.27%)	97 (7.55%)	254 (9.91%)
Urine protein/creatinine ratio increased*	66 (5.16%)	65 (5.06%)	131 (5.11%)
Metabolism and nutrition disorders			
Hyperkalaemia*	148 (11.56%)	138 (10.75%)	286 (11.15%)
Musculoskeletal and connective tissue disorders			
Arthralgia*	35 (2.73%)	21 (1.64%)	56 (2.18%)
Back pain*	27 (2.11%)	26 (2.02%)	53 (2.07%)
Nervous system disorders			
Dizziness*	70 (5.47%)	63 (4.91%)	133 (5.19%)
Headache*	18 (1.41%)	30 (2.34%)	48 (1.87%)
Renal and urinary disorders			
Haematuria*	145 (11.33%)	104 (8.10%)	249 (9.71%)
Microalbuminuria*	26 (2.03%)	19 (1.48%)	45 (1.76%)
Proteinuria*	121 (9.45%)	84 (6.54%)	205 (8.00%)

Renal failure*	49 (3.83%)	38 (2.96%)	87 (3.39%)
Renal impairment*	148 (11.56%)	110 (8.57%)	258 (10.06%)
Respiratory, thoracic and mediastinal disorders			
Cough*	41 (3.20%)	25 (1.95%)	66 (2.57%)
Dyspnoea*	47 (3.67%)	46 (3.58%)	93 (3.63%)
Skin and subcutaneous tissue disorders			
Pruritus*	27 (2.11%)	10 (0.78%)	37 (1.44%)
Vascular disorders			
Hypertension*	42 (3.28%)	81 (6.31%)	123 (4.80%)
Hypotension*	176 (13.75%)	69 (5.37%)	245 (9.56%)

* Non-systematic Assessment

Conclusion:

Based on the results presented in this report, the following is concluded regarding the efficacy and safety of sacubitril/valsartan in symptomatic patients with HFpEF, NYHA functional class II to IV and LVEF > 40%:

The study met one of its two primary endpoints. This study confirms the NT-proBNP lowering effect of sacubitril/valsartan, demonstrating a statistically significant 16% additional NT-proBNP reduction from baseline at Week 12 compared to the IMT group.

The study did not meet its second primary endpoint of improving 6MWD at Week 24, demonstrating a modest overall improvement in 6MWD of approximately 10-12 meters, and with no significant treatment difference.

Secondary endpoints demonstrated:
There were large symptom improvements from baseline in both treatment groups, as indicated by a 12-point increase in KCCQ CSS at Week 24. The study did not show a significant treatment difference in the KCCQ CSS change from baseline at Week 24, with a numerically greater effect in

the sacubitril/valsartan group of 0.5 points. Change from baseline in NYHA class at Week 24 was found to be similar between the two treatment groups.

All other secondary endpoints: change from baseline to Week 24 in KCCQ OSS, SF-36 PCS, 6MWD 30-meter responder analyses, and KCCQ CSS 5-point responder analyses showed neutral results with, at most numerical benefits of sacubitril/valsartan over IMT.

All sensitivity and subgroup analyses demonstrated consistency across the efficacy parameters. The safety profile of sacubitril/valsartan in this HFpEF population was comparable to the established safety profile in patients with HFpEF and HFrEF in previous studies. The lower incidence of cardiac failure SAEs in the sacubitril/valsartan group compared to the IMT group was consistent with less events of worsening HF on sacubitril/valsartan. The annualized rate of eGFR decline was significantly lower in the sacubitril/valsartan group compared to the IMT group. Sacubitril/valsartan was associated with more hypotension early after treatment initiation, and the rates of discontinuation of study medication were higher in the sacubitril/valsartan group, especially compared to placebo in the No RASi stratum.

Date of Clinical Trial Report

12-March-2020